REMARKS

Reconsideration of the application is respectfully requested.

Previously pending claims 132-140 have been cancelled. Claims 194-204 are pending and under examination.

Rejection under 35 USC Section 103

Claims 132-140 stand rejected as obvious over Clapperton *et al.* To expedite the prosecution of the application, these claims were cancelled. The rejection is therefore moot.

Method claims 194-201 stand rejected as obvious over Chang in view of Clapperton. The Examiner states that Chang teaches anti-platelet therapy using procyanidin oligomers, and Clapperton teaches that cocoa contains procyanidins. The Examiner also states that the claims as written embrace the inventions of Chang and Clapperton. Applicants respectfully traverse the rejection.

Applicants respectfully submit that Chang and Clapperton do not "embrace" the present invention, and Chang does not "teach" anti-platelet therapy—these statements imply that claims 194-201 lack novelty over the cited prior art. However, the Examiner has acknowledged that the present claims are novel—the only outstanding prior art rejection is based on obviousness.

Thus, Applicants' claims recite a method of anti-platelet therapy and the issue is whether the method would have been obvious over Chang (disclosing certain *in vitro* experiments) in view of Clapperton (disclosing certain cocoa extracts). Applicants have discovered unexpected effects of the procyanidin monomers and/or oligomers on several mechanisms and molecules involved in platelet activation and aggregation, *i.e.*, the compounds (i) increase nitric oxide (NO) synthesis (*see e.g.* specification, pages 15-16); (ii) increase prostacyclin (PGI_2) release by endothelial cells (*see e.g.* specification, Example 13, pages 47-50, Figure 19A); and (iii) decrease prostaglandin (PGE_2) release by endothelial cells (*see e.g.* specification, Example 13, pages 47-50, Figure 19B). Practicing Applicants' method claims results in the inhibition of platelet activation and aggregation in a human—activation of the GPIIbIIIa receptor for adhesive proteins is inhibited, the expression of P-selectin is reduced, and platelet granule formation is decreased (*see* specification, Example 14, pages 50-56 and Figures 21 and 22). Receptor GPIIbIIIa and P-selectin, which are present on the surface of activated platelets, and platelet

granules, which are secreted into the plasma, are the direct arbiters of platelet aggregation. None of these effects were expected from the teachings of Chang and Clapperton.

As discussed in the attached declaration by Dr. Debra A. Pearson [hereinafter "Pearson Declaration"], "an agent that affects several [platelet activation and aggregation signaling] pathways ...[is] therapeutically most advantageous" (*see* Pearson Declaration, par. 8). As discussed in par. 9-17 of the Pearson Declaration, the presently claimed therapy is "an impressive approach in that it positively affects numerous pathways as well as the interaction of platelets with endothelial cells" (par. 9), and is "much more beneficial than ... the effect caused by aspirin anti-platelet therapy, which affects cyclo-oxygenase activity and thus thromboxane synthesis" (par 9). After reviewing the beneficial effects of the claimed therapy and the Chang article, Dr. Pearson concludes that a person of skill in the art "would not have expected, from the article, that multiple beneficial effects could be achieved with an anti-platelet therapy administering procyanidins" because "the experiments conducted by Chang *et al.* utilized isolated platelets and were focused on only one mechanism (thromboxane synthesis)" (*see* Pearson Declaration, par. 18). According to Dr. Pearson, because of the ***multiple beneficial effects*** of the claimed anti-platelet therapy, this approach represents a very exciting alternative to the known anti-platelet therapy with aspirin, which permanently inhibits platelet TXA_2 synthesis (*see* Pearson Declaration, par. 19). In sum, the efficacy and benefits of the anti-platelet therapy recited in claims 194-201 are not suggested by the Chang article. Clapperton adds nothing more to the teaching of Chang because it does not disclose any therapeutic effects of procyanidins.

The Examiner appears to acknowledge the unexpected benefits of the present invention, but states that the claims do not recite the mechanisms of action (March 26, 2003 Official Action, page 4, last sentence above title "Double Patenting Rejection"). It is well established, however, that unexpected benefits need not be recited in the claims.

In view of the above statements, and the attached Pearson Declaration, Applicants believe that the withdrawal of the obviousness rejection of claims 194-201 is in order. An action to that effect is respectfully requested.

Double Patenting Rejection

Claims 132-140 and claims 194-201 are rejected as unpatentable over the claims of the U.S. Pat. No. 6,469,053. The rejection is moot regarding cancelled claims 132-140. With respect to claims 194-201, Applicants respectfully traverse.

The claims of the '053 patent are directed to the therapeutic methods achieved by administering a *methylated* cocoa procyanidin, *i.e.*, a derivative of the cocoa procyanidin. The present claims are directed to the compounds that re *not* methylated and are chemically different compounds. It would not have been obvious that the removal of methyl groups would result in compounds that are therapeutically effective for anti-platelet therapy. Therefore, withdrawal of the rejection is respectfully requested.

Upon finding of allowable subject matter, Applicants intend to file a Terminal Disclaimer over the claims of the U.S. Appl. Ser. No. 09/717,893.

CONCLUSION

In view of the above amendments and remarks, Applicants believe that the application is now in condition for allowance. A notice to that effect is respectfully requested.

Date: June 28, 2003

Respectfully submitted,

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Docket No. 1010-101US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Leo J. Romanczyk, Jr. et al.

Filed: December 10, 1999 Group Art Unit: 1626

Serial No: 09/459,171 Examiner: T. Solola

For: THE USE OF PROCYANIDINS IN THE MAINTENANCE OF VASCULAR HEALTH AND MODULATION OF THE INFLAMMATORY RESPONSE

DEBRA A. PEARSON DECLARATION

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. My name is Debra A. Pearson. I am an Assistant Professor at the University of Wisconsin Green Bay, Department of Human Biology, ES 301, 2420 Nicolet Drive, Green Bay, WI 54311.
2. I have obtained a Ph.D. degree in Nutrition from the University of California, Davis. A copy of my Curriculum Vitae is enclosed.
3. My research interests include platelet activation and aggregation. In that respect, I am knowledgeable about the published literature and the suitable experimental techniques in this area of research.
4. I am not an inventor of the above-identified patent application nor do I derive any interest from it.
5. In the period of 1995 to 1999, I have received partial funding from Mars, Incorporated, the assignee of the above-identified patent

application. I am no longer receiving the funding nor is such funding contemplated.

6. I have reviewed the text of the above-identified patent application, the presently pending patent claims, a copy of the Official Action mailed March 26, 2003, and the Chang *et al.* article (Inhibition of Platelet Aggregation and Arachidonate Metabolism in Platelets by Procyanidins; Prostaglandins Leukotrienes and Essential Fatty Acids (1989) 38: 181-188).

7. I understand that the patent claims are directed to a method of anti-platelet therapy or prophylaxis of a human or a veterinary animal by administration of procyanidins, and that the United States Patent and Trademark Office has rejected these claims because of the disclosure of the Chang *et al.* article. I was asked by Mars, Incorporated to evaluate the disclosure of Chang *et al.* In that respect, I was advised by the attorney for Mars, Incorporated that the disclosure of Chang *et al.* article should be considered as of April 1996, which I understand to be the earliest filing date of the above patent application.

8. Platelet activation and aggregation involves many complex mechanisms including multiple membrane receptors, second-messenger molecules and signaling pathways. These events require cellular interactions not only among the platelets but also between the platelets and the endothelial cells. Although the underlying mechanisms complement each other, platelet agonists and inhibitors, both physiologic and pharmacologic, differentially affect the various signaling pathways involved in platelet aggregation. In some cases, a platelet inhibitor may only affect one signaling pathway and have no effect on other pathways. For example, an inhibitor of thromboxane A_2 (TXA_2) synthesis pathway may be ineffective on the nitric oxide (NO) synthesis or other signaling pathways. The various pathways involved in

platelet aggregation provide an opportunity for numerous agents, at numerous points, to modulate platelet function. An agent that affects several pathways, however, would be therapeutically most advantageous.

9. Based on my review of the experimental results compiled by the inventors of the above-identified patent application, I find the anti-platelet therapy with procyanidins an impressive approach in that it positively affects numerous pathways as well as the interaction of platelets with endothelial cells. Such multifaceted effects on platelet activation and aggregation are much more beneficial than, for example, the effect caused by aspirin anti-platelet therapy, which affects cyclooxygenase activity and thus thromboxane synthesis.

10. As I discuss in more detail below, I would not have expected from the Chang *et al.* article that the anti-platelet therapy with procyanidins would have such beneficial multifaceted effects.

11. First, procyanidins increase nitric oxide (NO) synthesis as shown at pages 15-16 of the patent application. Based on the disclosure of Chang *et al*, I would not have expected any NO effects because the experiments used by Chang *et al.* were not designed to study and measure NO production nor is there any discussion to that effect in the article.

12. NO suppresses platelet activation by activating guanylyl cyclase (GC), enhancing Ca-dependent refilling of calcium stores, and inhibiting activation of PI3K. The former two mediate second-order effects resulting in suppression of calcium influx and leading to suppression of P-selectin expression and of expression of the active conformation of GPIIb/IIIa receptor. This chain of events results in inhibition of platelet aggregation and is independent from the TXA_2 pathway.

13. Second, procyanidins increase an eicosanoid, prostacyclin (PGI_2) release by endothelial cells as shown on pages 47 50, and Figure 19A, of the patent application. I would not have expected this effect after reading the Chang *et al.* article because endothelial cells (which produce PGI_2) were not utilized in Chang's experiments. Chang experimented with platelets in isolation (*see e.g.* page 182, 1st par.) excluding endothelial cells which have a critical role in modulating platelet aggregation and thrombus formation.

14. The presence of PGI_2 in the blood is beneficial since this molecule binds to a platelet membrane receptor and elevates platelet cyclic AMP (cAMP) concentration, which leads to inactivation of platelet myosin kinase, and thus reduces actin-myosin interaction, platelet contraction and granule secretion. This chain of events is independent from the TXA_2 pathway.

15. Third, procyanidins decrease prostaglandin (PGE_2) release by endothelial cells as shown at pages 47-50, and Figure 19B, of the patent application. Again, because Chang *et al.* have not conducted experiments in the presence of, or with, endothelial cells, I would not have expected, in April 1996, that the compounds would have had any effect on prostaglandin.

16. Reduction of prostaglandin is beneficial since the molecule appears to be involved in platelet aggregation by priming protein kinase C and inhibiting cAMP formation, which is independent from the TXA_2 synthesis pathway.

17. Finally, as shown in the Example 14, pages 50-56 and Figures 21 and 22, of the patent application, procyanidins inhibit platelet activation and aggregation upon administration to a human. Activation of the GPIIbIIIa receptor for adhesive proteins is inhibited, the expression of P-selectin is reduced, and platelet granule formation is decreased. Receptor GPIIbIIIa and P-selectin,

which are present on the surface of activated platelets, and platelet granules, which are secreted into the plasma, directly affect platelet aggregation.

18. Because the experiments conducted by Chang *et al.* utilized isolated platelets and were focused only on one mechanism (thromboxane synthesis), I would not have expected, from the article, that multiple beneficial effects could be achieved with an anti-platelet therapy administering procyanidins.

19. As mentioned in paragraph 9, aspirin acts by permanently inhibiting platelet TXA_2 synthesis. However, it is well accepted in the field that aspirin is far from being the solution for preventing platelet aggregation, and alternatives are being actively pursued. The anti-platelet therapy with procyanidins is a very exiting alternative given its multiple beneficial effects, none of which could have been predicted from the Chang *et al* article.

20. I declare that the above statements are true to the best of my knowledge.

Date: June 30, 2003

Debra Pearson PhD

Dr. Debra A. Pearson

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EDUCATION

Ph.D., Nutrition, University of California, Davis. Degree July 1998 Dissertation: Vascular targets and actions of plant phenolic compounds. Advisors: Dr. J. Bruce German and Dr. Edwin N. Frankel.

M.S., Nutritional Biochemistry, University of California, Davis, June 1995. Thesis: Inhibition of low density lipoprotein oxidation by rosemary and green tea phenolics. Advisor: Dr. J. Bruce German

D.C., National College of Chiropractic, Lombard, Illinois, April 1984.

B.S., Biological Sciences, National College of Chiropractic, Lombard, Illinois, December 1981.

California Community College Credential, Biological Sciences, 1986.

EMPLOYMENT

Assistant Professor, College of Human Biology, University of Wisconsin-Green Bay, Green Bay, WI. Courses: Nutritional Biochemistry, Human Nutrition, Life Cycle Nutrition, Advanced Nutrition and Metabolism, Food and Nutritional Health. 9/98 – present.

Associate-In, Department of Veterinary Medicine, Molecular Biosciences, University of California, Davis. Course: Physiological Biochemistry. 9/92-3/93

Instructor, Department of Biology and Health Sciences, DeAnza College, Cupertino, California. Courses: Human Anatomy and Physiology, Human Biology, Nursing Physiology Update.
4/86-6/94

RESEARCH GRANTS

2002 $7,938 Principle investigator, conjugated linoleic acid and fatty acid analysis of milk and
cheese from grass-grazing and conventional dairy farms. (US Department of Agriculture, Sustainable Agriculture Research and Education Program (USDA-SARE)).

1997 $18,000 Co-authored a research grant for studying plant phenolic antioixdant activity using an endothelial cell cuture system. Designed, and conducted the research, supervised student research assistants. (Biodelta Inc., Sacramento, California).

1996-97 $40,000 Co-authored a research grant for testing the antioxidant activities of grape seed extracts using a metal catalyzed LDL oxidation system. Designed, and conducted the research, supervised student research assistants. (Second Nature Technologies Inc., Mill Valley, California).

1993-96 $125,000 Co-authored a research grant for studying the antioxidant activities of plant phenolics. Designed and conducted the research using an endothelial cell culture system to mediate oxidation. (Nestle, Lausanne, Switzerland).

PROFESSIONAL AFFILIATIONS
American Institute of Nutrition

PUBLICATIONS

Holt, R.R.; Schramm, D.D.; Lazarus, S.A.; Fraga, C.G.; Wang, J.F.; Rein, D.; Pearson, D.A.; Schmitz, H.H.; Keen, C.L. Potential Effects of Flavanol-rich chocolate and cocoa on cardiovascular health in humans. *American Chemical Society* (in press).

Pearson, D.A.; Paglieroni,T.G.; Rein, D.; Wun, T.; Schramm, D.; Wang, J.F.; Holt, R.R.; Gosselin, R.; Schmitz, H.H.; Keen, C.L. 2002. The Effects of Flavanol-Rich Cocoa and Aspirin on ex vivo Platelet Function. *Thrombosis Research*. 106:191-197.

Pearson, D.A.; Schmitz, H.H.; Lazarus, S.A.; Keen, C.L. 2001. Chapter in a volume of Methods in Enzymology: Flavonoids and Other Polyphenols. Editor, Lester Packer. Chapter Title: *Inhibition of in vitro low-density lipoprotein oxidation by oligomeric procyanidins present in chocolate and cocoas*. Academic Press, 2001, Vol. 335: 350-360.

Rein, D.; Paglieroni, T.G.; Pearson, D.A.; Wun, T.; Schmitz, H.H.; Gosselin, R.; Keen, C.L. 2000. Cocoa and wine polyphenols modulate platelet activation and function. *J. Nutr.* 130: 2120S-2126S.

Rein, D.; Paglieroni, T.G.; Wun, T.; Pearson, D.A.; Schmitz, H.H.; Gosselin, R.; Keen, C.L. 2000. Cocoa inhibits platelet activation and function. *Am J Clin Nutr.* 72: 30-35.

Bearden, M.M.; Pearson, D.A.; Rein, D.; Chevaux, K.A.; Carpenter, D.R.; Keen, C.L.; Schmitz, H.H. 2000. Book Chapter in Caffeinated Beverages: Health Benefits, Physiological Effects and Chemistry. Chapter Title: *Potential cardiovascular benefits of procyanidins present in chocolate and cocoa.* American Chemical Society, 2000, Vol. 754: 177-186.

Pearson, D.A.; Tan, C.H.; German, J.B.; Davis, P.A.; Gershwin, M.E. 1999. Apple juice inhibits human low-density lipoprotein oxidation. *Life Sciences* 64: 1913-1920.

Meyer, A.S.; Donovan J.L.; Pearson, D.A.; Waterhouse, A.L.; Frankel, E.N. 1998. Fruit Hydroxycinnamic Acids Inhibit Human Low-Density Lipoprotein Oxidation in Vitro. *J Agric Food Chem* 46: 1783-1787.

Pearson, D.A.; Frankel, E.N.; Aeschbach, R.; German, J.B. 1998. Inhibition of endothelial cell mediated low density lipoprotein oxidation by green tea extracts. *J Agric Food Chem* 46: 1445-1449.

Meyer, A.S.; Yi, O.-S.; Pearson, D.A.; Waterhouse, A.L.; Frankel, E.N. 1997 Inhibition of human low-density lipoprotein oxidation in relation to composition of phenolic antioxidants in grapes (*Vitis Vinifera*). *J Agric Food Chem* 45: 1638-1643.

Schramm, D.D.; Pearson, D.A., German, J.B. 1997. Endothelial cell basal prostacyclin release is stimulated by wine in vitro: One mechanism that may mediate the vasoprotective effects of wine. *J Nutr Biochem* 8: 647-651.

Pearson, D.A.; Frankel, E.N.; Aeschbach, R.; German, J.B. 1997. Inhibition of endothelial cell mediated LDL oxidation by rosemary and plant phenolics. *J Agric Food Chem* 45: 578-582.

In Preparation / Submitted:

Pearson, D.A.; Rein, D.; Frankel E.N.; German, J.B.; Rutledge, J.C. Effect of a vitamin E or catechin enriched diet on LDL accumulation in the artery wall of the hamster.

Yoshida, S.H., Pearson, D.A., Hochderffer, L.J., Siu, J., Shaffrath, J.D., Schmitz, H.H., Applegate, E.A., German, J.B., Gershwin, M.E., Keen, C.L., Emenhiser, C., Schwartz, S.J. Effect of an antioxidant-rich supplement on eicosanoid production and platelet aggregation in runners.

ABSTRACTS AND PRESENTATIONS

Pearson, D.A. 2002. Cocoa Flavonoids and Platelet Reactivity. Presented at The Flavanoid Workshop, March 1-2, University of California-Davis, Davis, California

Pearson, D.A., Paglieroni, T.; Rein, D.; Wun, T.; Gossselin, R.; Schramm, D.D.; Wang, J.; Schmitz, H.H.; Holt, R.R.; Keen, C.L. 2001. Effect of aspirin and cocoa procyanidins on platelet-dependent hemostasis. *FASEB Journal,* 15: A285.

Schmitz, H.H.; Rein, D.; Pearson, D.A.; Keen, C.L. 1999. Cacoa oligomeric procyanidins decrease LDL oxidation and lipoxidase activity. *FASEB Journal* 13: A546.

Rein, D.; Pearson, D.A.; Paglieroni, T.; Wun, T.; Schmitz, H.H.; Keen, C.L. 1999. Modulation of platelet activation by cacao or red wine polyphenols in vitro. *FASEB Journal* 13: A886.

Wun, T.; Rein, D.; Pearson, D.A.; Paglieroni, T.; Gosselin, R.; Keen, C.L. 1998.The effect of dealcoholized red wine on platelet reactivity in vivo. *Blood* 92 (Supplement 1): 75b.

Rein, D.; Pearson, D.A.; Schmitz, H.H.; Keen, C.L. 1998. Cocoa oligomeric procyanidins decrease lipoxidase activity and LDL oxidation. *Rev Parm Bioquim* Univ Sao Paulo 34: PS 1534.

Rein, D.; Pearson, D.A.; Paglieroni, T.; Wun, T.; Schmitz, H.H.; Keen, C.L. 1998. Modulation of platelet activation by dietary wine phenols in vitro. *Rev Parm Bioquim.* Univ Sao Paulo 34: PS 1535.

Pearson, D.A.; Rein, D.; Frankel E.N.; German, J.B.; Rutledge, J.C. 1997. Effect of a vitamin E or catechin enriched diet on LDL accumulation in the artery wall of the hamster. Presented at the annual meeting of the American Oil Chemists' Society, Seattle, WA.

Pearson D.A.; Frankel E.N.; Aeschbach R.; German J.B. 1996. Inhibition of endothelial cell mediated LDL oxidation by green tea extracts. FASEB Journal 10: A476.

Pearson D.A.; Frankel E.N.; Aeschbach R.; German J.B. 1995.Inhibition of endothelial cell mediated LDL oxidation by rosemary and plant phenolics. FASEB Journal 9: A576.

CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that these papers are being facsimile transferred to the United States Patent and Trademark Office on the date shown below.
Date: July 28, 2003
By: Nada Jain

Docket No. 1010-101US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Leo J. Romanczyk, Jr. et al.		
Filed:	December 10, 1999	Group Art Unit:	1626
Serial No:	09/459,171	Examiner:	T. Solola

For: COMPOSITIONS FOR, AND METHODS OF, ANTI-PLATELET THERAPY

NOTICE OF APPEAL

MAIL STOP: After Final
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby appeal to the Board of Appeals from the Final Rejection mailed March 26, 2003 of the Primary Examiner finally rejecting claims 132-140 and 194-204.

The items checked below are appropriate:

☒ A Request for Extension of Time is filed concurrently herewith, with requisite fee along with an Amendment under 37 C.F.R. § 1.116, meeting the present response deadline of July 28, 2003. Should additional extensions of time be required, such extensions are requested and the Commissioner is authorized to charge the deposit account provided below.

☒ The fee of $320.00

☐ is enclosed.

☒ should be charged to Deposit Account No. 50-2549.

The Commissioner is authorized to charge any additional fee or credit overpayment in connection with this communication to Deposit Account No. 50-2549. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Date: July 28, 2003

Nada Jain
Reg. No. 41, 431

NADA JAIN, P.C.
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